Preparation of Aryl Intermediates

APPLICATION DATA

This application claims benefit to US provisional application no. 60/428,618 filed November 22, 2002.

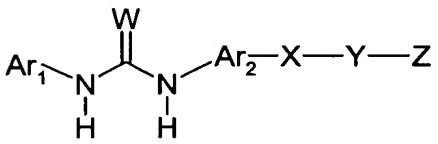
FIELD OF INVENTION

This invention relates to the synthesis of aryl intermediate compounds which are useful in the production of pharmaceutically active heteroaryl urea compounds.

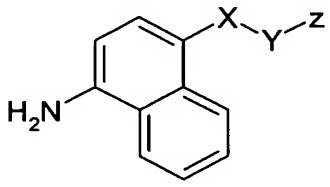
BACKGROUND OF THE INVENTION

Aryl- and heteroaryl-substituted ureas have been described as inhibitors of cytokine production. These inhibitors are described as effective therapeutics in cytokine-mediated diseases, including inflammatory and autoimmune diseases.

U.S. Patent no. 6,358,945 describes cytokine inhibiting ureas of the following formula:

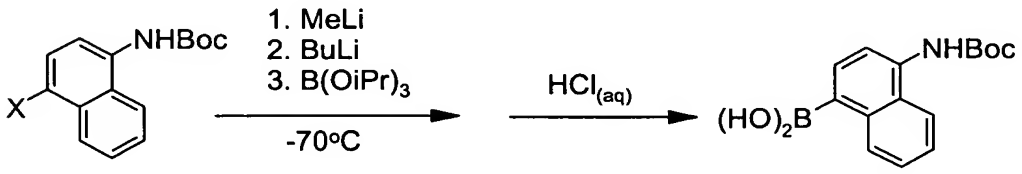


An intermediate required to prepare preferred compounds described therein has a 1,4-disubstituted naphthalene as Ar_2 and is illustrated in the formula below.



The preparation of these intermediates require the coupling of the naphthyl ring with X. Preferred X include aryl and heteroaryl groups. Previously described methods, including U.S. Patent no. 6,358,945 achieves the coupling of these aromatic residues by using a coupling reaction catalyzed by a transition metal, such as palladium, in the presence of a ligand, such as triphenyl phosphine. Coupling methods include Stille coupling, requiring the preparation of a tributylstannyl intermediate, or a Suzuki coupling, requiring the preparation of an aryl boronic acid intermediate (Scheme I).

Scheme I



X = Br or I

The aryl boronic acid intermediate shown in I has previously been prepared via Br-Li exchange at -70°C. It is desirable to develop a procedure without using cryogenic condition for large-scale or industrial scale production.

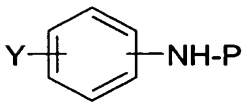
Kitigawa *et al.* disclose a method for preparing trialkyl magnesates useful for halogen-metal exchange (*Angew. Chem. Int. Ed.* 2000, 39, No. 14 2481-2483). No example in the paper implied the applicability of this method to the preparation of A, which has an acidic proton on the nitrogen.

BRIEF SUMMARY OF THE INVENTION

It is therefore an object of the invention to provide a non-cryogenic synthesis for aryl intermediate compounds such as aryl boronic acids which are useful in the production of heteroaryl urea compounds.

DETAILED DESCRIPTION OF THE INVENTION

In a broad generic aspect, there is provided a method of making a compound of the formula (A):



(A);

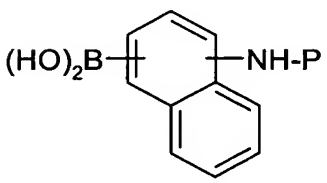
wherein the formula (A):

P is a nitrogen protecting group compatible with Grignard reagents, preferably P is chosen from Boc, Cbz, -CO_2Me, -Ac, -Bn; preferably P is Boc;

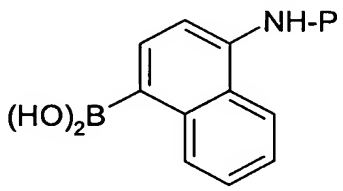
Y is chosen from -$B(OH)_2$, -CHR'-OH, -CR'_2-OH, alkyl, alkene and acyl;

E is an electrophile as defined herein below;

the phenyl ring in (A) is optionally benzo-fused to form naphthyl wherein substituents Y or NH-P can be independently at any position on each of the one or two rings, where the phenyl is not benzo-fused substitution can be para, meta or ortho, preferably para; preferably formula (A) is



; more preferably formula (A) is:

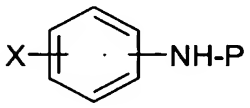


;

said method comprising, in a one pot reaction:

reacting a compound of the formula (B) with 2 equivalents of R_3MgLi, wherein and R is C_{1-5} alkyl, preferably n-butyl, in an aprotic solvent at a temperature between –40^{0}C to 40^{0}C, preferably -20^{0}C to 0^{0}C, more preferably 0^{0}C, the aprotic solvent is, for example,

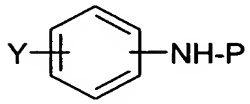
dioxane, diethoxymethane, methylTHF, THF, diisopropylether, hydrocarbons including hexanes, heptane, isooctane, cyclohexane, xylenes, Toluene, dichloromethane, DME, MTBE, or mixtures thereof, preferably the aprotic solvent is THF;



(B) wherein X is bromine or iodine, preferably bromine,

subsequently adding an electrophile E, such as, for example, $B(OCH_3)_3$, aldehydes such as CH_3CHO, ArylCHO, ketones such as CH_3COCH_3, $ArylCOCH_3$, halide such as $CH_2=CHCH_2Br$, CH_3I, or esters such as CH_3CO_2Et, preferably E is $B(OCH_3)_3$, further non-limiting examples of E are set forth in the table below;

to produce a compound of the formula (A)



(A).

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art.

RT or rt – room temperature;

n-BuLi - n-Butyllithium

DME - 1,2-Dimethoxyethane

THF - Tetrahydrofuran.

Boc - tert-Butoxycarbonyl.

Cbz - Benzyloxycarbonyl.

Ac - Acetyl.

Bn - Benzyl.

MeLi – methyllithium.

Unless otherwise noted, alkyl shall be understood to mean C_{1-10} alkyl chain, preferably C_{1-5} alkyl, branched or unbranched. An alkene is a partially unsaturated alkyl.

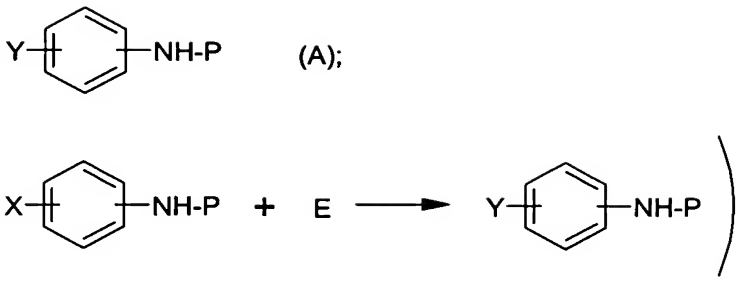
Ester, acyl, ketone, aldehyde and alkene shall be understood to mean an alkyl chain as herein above defined, with the respective functional group.

The term "aryl" as used herein shall be understood to mean aromatic carbocycle or heteroaryl as defined herein. Preferred carbocycles include phenyl and naphthyl. Each aryl or heteroaryl unless otherwise specified includes it's partially or fully hydrogenated derivative. For example, naphthyl may include it's hydrogenated derivatives such as tetrahydranaphthyl. Other partially or fully hydrogenated derivatives of the aryl and heteroaryl compounds described herein will be apparent to one of ordinary skill in the art.

It shall be understood, that the definitions E and Y have the following corresponding relationship as seen in the table and scheme below:

E	Y
$B(O\text{-}C_{1-5}alkyl)_3$	$-B(OH)_2$
R'HC=O	-CHR'-OH
$R'_2C(=O)$	$-CR'_2$-OH
R'X	-R'
$R'CO_2R'$	R'C(=O)-
R'_3SnX	SnR'_3
R'_3SiX	R'_3Si
$R'_2(OR')SiX$ or $(R'_2SiO)_3$	$SiR'_2(OR')$

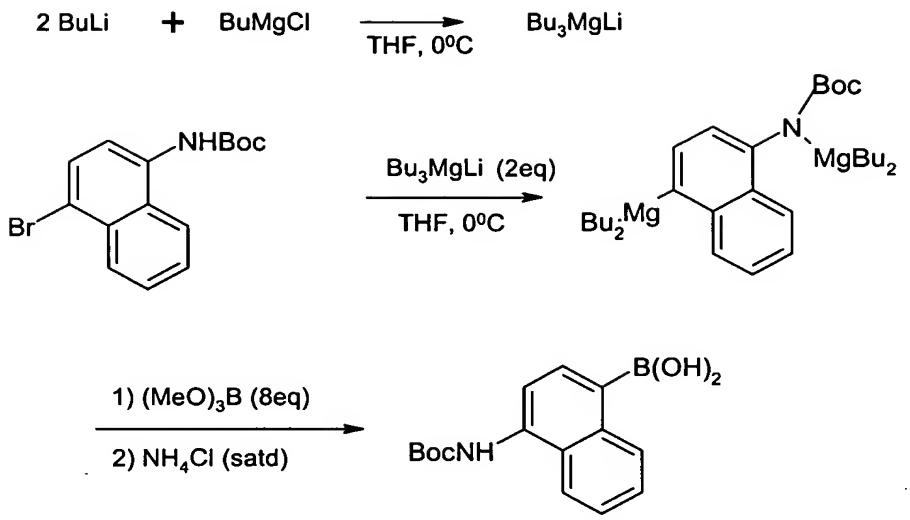
Wherein R' can be alkyl or aryl as defined herein, X is halogen and for $B(O\text{-}C_{1-5}alkyl)_3$ the C_{1-5}alkyl includes all C_{1-5}alkyl, preferably methyl, ethyl, propyl and butyl, more preferably methyl.



The compounds of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated by the invention.

In order that this invention be more fully understood, the following examples are set forth in the overall reaction scheme below. These examples are for the purpose of illustrating preferred embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

Example: Synthesis of N-Boc-4-amino-1-naphthalene boronic acid



In a dry flask under Argon was added butylmagnesium chloride (2.0 M in THF, 2.0 mL, 4.0 mmol) and anhydrous THF (10 mL). The solution was cooled to –5 °C and butyllithium (1.6 M in hexane, 5.0 mL, 8.0 mmol) was added dropwise while the temperature was kept below 0 °C. After the resulting solution was stirred at 0 °C for 0.5 h, the temperature was lowered to –5 °C. N-Boc-4-bromo-1-aminonaphthalene (0.64g, 2.0 mmol) was dissolved in anhydrous THF(10 mL) and added dropwise while the temperature was kept below 0 °C. The solution was stirred at 0 °C for 0.5 h. HPLC of a sample taken from the solution and quenched with MeOH indicated that no starting material was left. The temperature was lowered to –5 °C and trimethyl borate(2.5 mL, 22.0 mmol) was added slowly. After the mixture was stirred at 0 °C for 2 h, ammonium chloride solution (saturated, 20 mL) was added and the mixture was stirred at 21 °C for 0.5 h. The pH of the mixture was adjusted to 7 with sodium bicarbonate and the mixture was stirred at 21 °C for 18 h. Ethyl acetate (10 mL) was added and the mixture was stirred for 0.5 h. The organic layer was separated and dried with magnesium sulfate. The solvent was removed under vacuum and then hexane (60 mL) was added and the resulting slurry was stirred for 0.5 h. Filtration and hexane (10 mL) wash gave the title compound as a white solid (0.46g, 80.5% pure, 65% yield).